

## CASE REPORT

# Pure white cell aplasia an exceptional condition in the immunological conundrum of thymomas: Responses to immunosuppression and literature review

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## Abstract

Thymomas are tumours frequently associated with autoimmune manifestations or immunodeficiencies like Good syndrome. In rare cases, pure white cells aplasia (PWCA) has been described in association with thymomas. PWCA is characterized by agranulocytosis of autoimmune background primary refractory to granulocyte colony-stimulating factor (G-CSF). It is necessary the use of immunosuppressor to allow granulocyte recovery. Without treatment, it could be fatal.

## KEYWORDS

agranulocytosis, granulocytopenia and good's syndrome, pure white cell aplasia, thymoma

## 1 | INTRODUCTION

PWCA is a hematologic disorder characterized by agranulocytosis with absence of myeloid precursors in bone marrow with an erythropoiesis and megakaryopoiesis preserved. It has been associated with drugs, infectious diseases and autoimmunity.<sup>1</sup> Thymomas and thymic carcinomas may present autoimmune phenomena fundamentally: myasthenia gravis (MG) up to 50% of the cases and pure red cell aplasia (PRCA) up to 5% of the cases.<sup>2</sup> However, the incidence of thymoma and PWCA is extremely rare by existing few reports.<sup>3</sup>

We conducted a search for articles registered in Pub-Med between 1950 and 2021, which were available in English. The keywords used were as follows: Thymoma, Pure White Cell Aplasia, Agranulocytosis, and Granulocytopenia.

## 2 | CASE

A 33-year-old male, with a history of admission to the intensive care unit for influenza A in 2016, consulted for skin lesions at primary care and was given treatment with amoxicillin/clavulanic acid and ibuprofen in October 2020. Three days later, he consulted the emergency department of our hospital due to the worsening of clinical symptoms with thermometric tympanic fever of 40.5°, blood pressure 123/67 mmHg, and heart rate 98 beats per minute. He had not taken any other medication or drugs previously. Examination revealed a 2 cm branching ulcer on the oral mucosa and four indurated skin lesions with an erythematous halo and necrotic center, suggestive of gangrenous ecthyma (Figure 1), the largest on the left hand measuring 3 cm in diameter.

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Laboratory tests on admission showed normal renal, liver, and thyroid function, C-reactive protein 3104.7 nmol/L (Normal Range 0–1100), procalcitonin 1400 ng/L (NR 0–100), hemoglobin 139 g/L (NR 130–160), platelets  $161 \times 10^9/L$  (NR 150–450), and leukocytes  $0.5 \times 10^9/L$  (NR 4.5–10) (Revised formula: 100% lymphocytes). IgG 4.79 g/L (NR 6–17), IgA 0.57 g/L (NR 0.7–4) IgM 0.69 g/L (NR 0.4–2.30), C3 and C4 normal. Anti-nuclear, anti-neutrophil (ANCA), anti-musk, and anti-acetylcholine antibodies were negative. Serology for HBV, HCV, and HIV were negative; he tested IgG + against EBV and CMV. Peripheral blood flow cytometry analysis showed CD4<sup>+</sup>/CD8<sup>+</sup> ratio inversion 0.56, low B lymphocytes, but no data suggestive of B/T clonality. Blood cultures, nasal swab for *S. aureus* as well as bacterial culture and PCR of skin lesions were negative. Bone marrow aspirate showed normal erythroid and megakaryocytic series. Granulocytic series represented 3.6% of the total cellularity, promyelocyte maturational arrest was observed (Figure 2). There was no evidence of dysplasia or increased blast cellularity, karyotype 46, XY. CT scan revealed an anterior mediastinal mass measuring  $47 \times 71 \times 60$  mm with no evidence of locoregional infiltration. A biopsy of the mass was performed with an anatomopathological result of mixed type AB thymoma (Figure 3).

On admission, empirical antibiotic therapy was started with piperacillin/tazobactam and daptomycin with the improvement of symptoms and resolution of fever in the



**FIGURE 1** Left hand skin lesion. Notice the necrotic centre surrounded by erythematous halo, this aspect is suspicious of gangrenous ecthyma

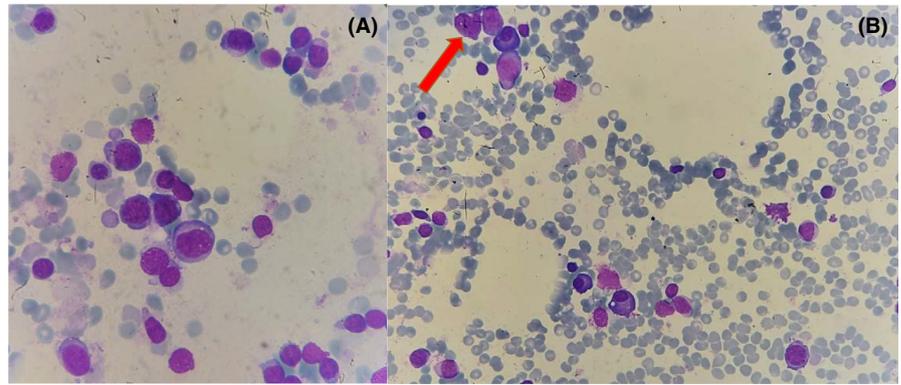
following days. With the initial diagnosis of agranulocytosis, G-CSF 480 mcg/24 h was added to the treatment for 13 days with no increase in the neutrophil count, so it was discontinued. Once the diagnosis of thymoma was confirmed and with the suspicion of related PWCA, single dose of intravenous Immunoglobulin G (IVIG) 1 g/Kg, and ciclosporine (CyA) with target levels 200–300 ng/dl were initiated. On Day +10, there were signs of granulocytic recovery: Neutrophils  $0.17 \times 10^9/L$  in peripheral blood; so, G-CSF was associated; on Day +14 from the start of CyA the patient reached neutrophils  $17 \times 10^9/L$ . Thymectomy was performed on Day +21, without remarkable incidents.

After thymectomy, CyA tapering was started. Six months later CyA was discontinued, neutrophil count remains still stable seven months after discontinuation: leukocytes  $7.5 \times 10^9/L$ , neutrophils  $4 \times 10^9/L$ , hemoglobin 148 g/L, and platelets  $185 \times 10^9/L$ . Immunoglobulin levels, CD4<sup>+</sup>/CD8<sup>+</sup> ratio and B lymphocytes returned to normal values. The patient has not presented any infectious, CyA-related or post-surgical complications during follow-up.

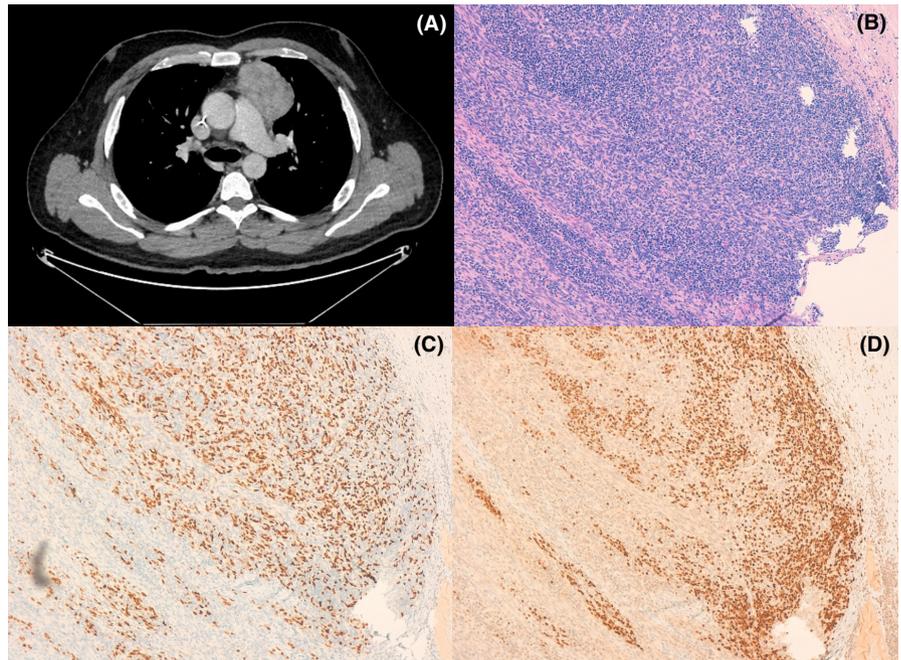
### 3 | DISCUSSION

Immunity may be impaired in patients with thymoma. Thymoma-associated immunodeficiency is known as Good's syndrome and includes hypogammaglobulinemia, decreased or absent B lymphocytes, CD4<sup>+</sup>/CD8<sup>+</sup> inversion, and decreased T lymphocytes. In addition, autoimmune manifestations may occur.<sup>4</sup> The etiology of thymoma related PWCA is still unknown, but it appears to have an autoimmune background. Growth inhibition of granulocytic and macrophage colony-forming units exposed to different concentrations of serum from these patients has been observed. This finding suggests the presence of an immunoglobulin against immature myeloid cells, indicating an alteration of B cells and humoral immunity.<sup>5</sup> Conversely, the response to anti-calceineurin immunosuppressors in these cases, as in PRCA, points to an alteration in T cells and cellular immunity.<sup>6</sup> Thymus is the organ where T-cell maturation and TCR gene rearrangement occurs. Besides, it is the place where negative selection of autoreactive T cells and positive selection of T cells capable of recognizing MHC presented antigens take place.<sup>7</sup> In this sense, several causal mechanisms for the loss of self-tolerance in thymoma patients have been proposed: (1) Immaturity of neoplastic T cells that would allow the escape of autoreactive lymphocytes, (2) Neoplastic genetic alterations that would predispose to the appearance of autoimmunity such as decreased expression of HLA-DR, and (3) Theory of combined dysregulation of cellular and

**FIGURE 2** Panel A bone marrow aspirate May-Grünwald Giemsa x100. Cellularity composed of lymphocytes and erythrocyte precursors. Panel B bone marrow aspirate May-Grünwald Giemsa x50. This section show plasmatic cells, lymphocytes and a granulocytic precursor (red arrow). Notice the absence of granulocytic mature forms



**FIGURE 3** Panel A CT scan showing an anterior mediastinal mass. Panel B Mass biopsy hematoxylin–eosin x10. neoplastic tissue resting on a fusocellular fibrous stroma composed of a rounded epithelial cellularity with an eosinophilic nucleolus. Panel C P63 immunohistochemistry x10. Neoplastic tissue positive. Panel D TdT immunohistochemistry x10. Immature T lymphocytes disposed in a reticular pattern



humoral immunity, an autoreactive T cell would activate a B cell to produce autoantibodies.<sup>8</sup>

Surgery to resect tumor tissue is the standard treatment for patients with thymoma. Thymectomy could resolve the autoimmune manifestations by removing the neoplastic tissue, which seems to provide the antigenic stimulus for autoreactive cells.

It has been reported the case of a patient with thymoma and granulocytopenia in whom a decrease in anti-pANCA antibody titer and elevation of granulocytes in peripheral blood was observed after thymectomy.<sup>9</sup> However, in other cases neutropenia has not resolved after thymectomy and a second line of treatment is necessary.<sup>10,11</sup> The medical treatment of these patients is not established currently due to low incidence of cases. Several strategies have been used to increase granulocyte counts (Table 1). GCS-F and IVIG normally have no impact in granulocytic count.<sup>12</sup> Of the 24 patients collected 13 survive, all of them receive some immunosuppressive treatment (CyA 6 patients, azathioprine 2, corticoid 2, alemtuzumab 1, chemotherapy 1, and plasmapheresis 1) which reinforces the idea of a

combined surgical and immunosuppressive treatment for these patients.

CyA has demonstrated favorable responses in these patients. It has been used with target trough levels of 200–400 ng/mL and monitoring toxicities. Granulocytic recovery occurs within 7–10 days. Maintenance treatment has usually been applied, with CyA tapering until its total suspension after 4–6 months.<sup>5,10</sup> Others have used extended treatment with CyA and prednisone in decreasing doses for up to 20 months after thymectomy.<sup>12</sup>

Alemtuzumab has been successfully used as an immunosuppressor in autoimmune bone marrow failures. In two cases of PWCA, alemtuzumab has achieved complete response in the first month.<sup>13</sup> Alemtuzumab has been useful in the treatment of a patient with PWCA and thymoma, after the failure of G-CSF and plasmapheresis, achieving granulocyte recovery in 12 days. However, agranulocytosis relapsed 5 months later and was treated with a new cycle of alemtuzumab associated with CyA and maintenance mycophenolate.<sup>14</sup>

TABLE 1 Pure White Cell Aplasia associated to thymoma reported in literature

CASE	REFERENCE	AGE	SEX	THYMOMA HISTOLOGY	BONE MARROW	DEBUT AND ALTERATIONS
1	Josse JH, 1958	73	F	Spindle cell	Hypoplastic y amegacarcocytosis	Fever and caquexia
2	Thiele H G, 1967	53	M	Spindle cell	Promyelocyte arrest	ND
3	Rogers BHJ, 1968	69	F	Spindle cell	Hypoplastic	Anemia, trombocytopenia bleeding and petechial Hypogammaglobulinaemia
4	Jacobson BM, 1971	70	F	Spindle cell	Promyelocyte arrest	Fever Hypogammaglobulinaemia ANA+
5	Young RH, 1977	68	F	Spindle cell	Myelopoiesis absent	Fever Hipogammaglobulinemia Reumatoid Factor+
6	Degos L, 1982	52	F	Spindle cell	Promyelocyte arrest	Recurrent infections Hypogammaglobulinaemia and absent B lymphocytes
7	Ackland SP, 1988	70	F	Metastasis malignant Spindle cell	Myelopoiesis absent	Pulmonary sepsis Hypogammaglobulinaemia Miastenia gravis
8	Weir AB, 1989	64	M	Spindle cell	Promyelocyte arrest	Fever Hypogammaglobulinaemia CLL
9	Nagashima S, 1989	58	M	Spindle cell	Promyelocyte arrest	Reordenamiento TCR $\beta$ ? Anti-AChR
10	Mathieson PW, 1990	46	F	Lymphoepitelial	Promyelocyte arrest	Mucotutaneus ulcers Hypogammaglobulinaemia Miastenia gravis
11	Postiglione K, 1995	68	F	Spindle cell	Promyelocyte arrest	Trombosis ANA+
12	Yip D, 1996	51	M	Spindle cell	Promyelocyte arrest	Fever Hypogammaglobulinaemia Anti-MUSK
13	Yip D, 1996	52	F	Spindle cell	Myelopoiesis absent	Fever, mucocutaneous ulcers ANA+
14	Crawford WW, 1999	59	M	Spindle cell	Myelopoiesis nearly absent	Diarrhea, dysphagia Hypogammaglobulinaemia CD4:CD8 inversion and low B lymphocytes
15	Fumeux Z, 2003	76	F	Cortical B2	Myelopoiesis absent	Fever and weight lose
16	Alvares CL, 2004	59	M	Spindle cell	Myelopoiesis absent	Fever and mucocutaneous ulcers Anti- AChR Hypocomplementemia
17	Jethava Y, 2011	45	M	AB thymoma	Myelopoiesis absent	Fever and sepsis Hypogammaglobulinaemia XI Factor deficiency
18	Akinosoglou K, 2014	70	F	Spindle cell	Promyelocyte arrest	Absent B lymphocytes Low IgA and IgM Cryptococcal infection
19	Okusu T, 2016	72	M	B2 thymoma	Granulocytic hypoplasia	<i>Candida albicans</i>
20	Olivera M, 2018	66	F	AB thymoma	Hypoplasia and Promyelocyte arrest, displastic	Recurrent infection Hypogammaglobulinaemia absent B lymphocytes
21	Kobayashi Y, 2018	63	M	Spindle cell	Myelopoiesis absent	Fever Hypogammaglobulinaemia
22	Uy K, 2019	65	F	Mixed AB2	Promyelocyte arrest	Fever and rash Hypogammaglobulinaemia
23	Case	33	M	Mixed AB	Promyelocyte arrest	Fever, mucocutaneous sepsis Hypogammaglobulinaemia CD4:CD8 inversion

Abbreviations: Anti-AChR, anti-acetilcholine antibody; Anti-MUSK, anti-smooth muscle antibody; CLL, Chronic Lymphocytic Leukemia; CyA, cyclosporine A; M, male; F, female; G-CSF, Granulocyte colony-stimulating factor; IVIG, intravenous immunoglobuline G; MMF, micophenolate mofetil; ND, no data; R, refractory; TCR, T-Cell receptor.

1°LINE THERAPY (DAYS UNTIL RESPONSE)	RELAPSE	2° (DAYS UNTIL RESPONSE)	SERUM INHIBITOR	EXITUS
Antibiotics (R)	-	-	-	Yes
-	-	-	-	Yes
Prednisone +Testosterone (R)	-	Thymectomy (R)	-	Yes
Splenectomy (R)	-	Prednisone +Isoniacide (R)	-	Yes
-	-	-	-	Yes
Thymectomy Prednisone and Cyclophosphamide (R)	-	Plasmapheresis (ND)	Yes	No
IVIG (R)	-	-	Yes	Yes
Vincristine +prednisone (6)	Yes	Vincristine +prednisone (14 days) Thymectomy (6 days)	Yes	Yes
Radiation (R)	-	Prednisone, thymectomy (?)	No	No
Plasmapheresis (R)	-	Azathioprine +prednisone (120 days)	Yes	No
G-CSF +IVIG + Prednisone (R)	-	Thymectomy, Plasmapheresis +Cyclophosphamide (7)	Yes	Yes
Prednisone, CHOP and thymectomy (R)	-	G-CSF (6 days) G-CSF maintenance	No	No
G-CSF, prednisone (R)	-	IVIG, cyclophosphamide (R)	-	Yes
Methylprednisolona, and Azathioprine (21) NO Thymectomy performed	-	-	-	No
Thymectomy +IVIG+ GCSF +Metilprednisolone pulse (7)	Yes	CyA, Metilprednisolone +G-CSF (3)	-	No
G-CSF (R) Plasmapheresis (R)	Yes	Alemtuzumab (12) Alemtuzumab +CyA + MMF +GCSF	Yes	No
CyA +Thymectomy (10)	Yes	CyA (7)	-	No
Dexamethasone +G-CSF +IVIG (20)	-	-	-	No
-	-	-	-	Yes
Thymectomy, IVIG and G-CSF (R)	-	CyA (>30 days)	-	No
G-CSF (R)	-	CyA (10)	Yes	No
Thymectomy (R)	-	CyA +G-CSF (7)	-	No
G-CSF (R)	-	CyA +IVIG (10)	-	No

A case has been described of a patient with MG thymectomized, who relapsed after 12 years with MG and de novo PWCA. In this case, plasmapheresis was started with the improvement of the MG symptoms as diagnosis, but there was no change in the granulocyte count after 15 sessions. Azathioprine 2.5 mg and prednisone mg/kg were started, obtaining an increase in the granulocyte count 4 months later.<sup>15</sup> It suggests that plasmapheresis alone is not a good option for the treatment of PWCA, and the use of concomitant immunosuppressor is needed.

Thymectomy is a major surgery with high complexity and infectious risks. We consider that the appropriate management would be the resolution of the PWCA prior to surgery. According to our review, treatments with immunosuppressive drugs are associated with better outcome. In our patient, we have obtained a good response with CyA, which supports the existing literature as the most successful therapeutic option. Furthermore, it is a drug with a known safety profile, extensive experience in its use and the possibility of measuring levels. Therefore, we suggest the use of CyA as a first-line drug with the concomitant use of G-CSF from granulocyte recovery onwards. Long-term follow-up of thymoma and immunological status is advisable because relapses have been observed in these patients.

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None.

#### CONFLICT OF INTEREST

The authors report no conflicts of interest associated with this publication.

#### AUTHOR CONTRIBUTIONS

Roberto Céspedes López is the main author, was involved in patient care, provided necessary data for the article, and manuscript preparation. Elena Amutio Díez is the main reviewer, was involved in manuscript preparation, checked grammatical and data errors, and patient care. Xabier Martín Martitegui was involved in patient care and provided data for the article. Amaia Balerdi Malcorra was involved in patient care. Lucía Insunza Oleaga was involved in patient care and provided data for the article. Javier Arzuaga Méndez was involved in patient care and provided data for the article. Maite Moreno Gámiz was involved in patient care and provided data for the article. Mónica Sainz Camín provided pathology images and their pathological description. Yoseba Aberasturi Plata provided pathology images and their pathological description. Juan Carlos García-Ruíz checked the manuscript for grammatical and scientific errors.

#### CONSENT

Appropriate informed consent was taken for the publication of this report and the associated images. The authors have confirmed that the patient consent has been signed and collected in accordance with the journal consent policy.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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